Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Leukaemia Section

Mini Review

del(11)(q23q23) MLL/ARHGEF12

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Clinics and pathology

Disease

Acute myeloid leukemia (AML)

Epidemiology

Two cases so far: a 38-year-old male patient with a history of occupational exposure to herbicides and a M4-AML, and a 77-year-old female patient with a M5a-AML (Kourlas et al., 2000; Shih el al., 2006).

Evolution

The M4-AML patient underwent complete remission, but died 6 months later from an unrelated cause.

Cytogenetics

Cytogenetics morphological

The del(11)(q23q23) has been missed by cytogenetic analysis; both cases were hyperploid with +8 and other abnormalities.

Genes involved and proteins

MLL

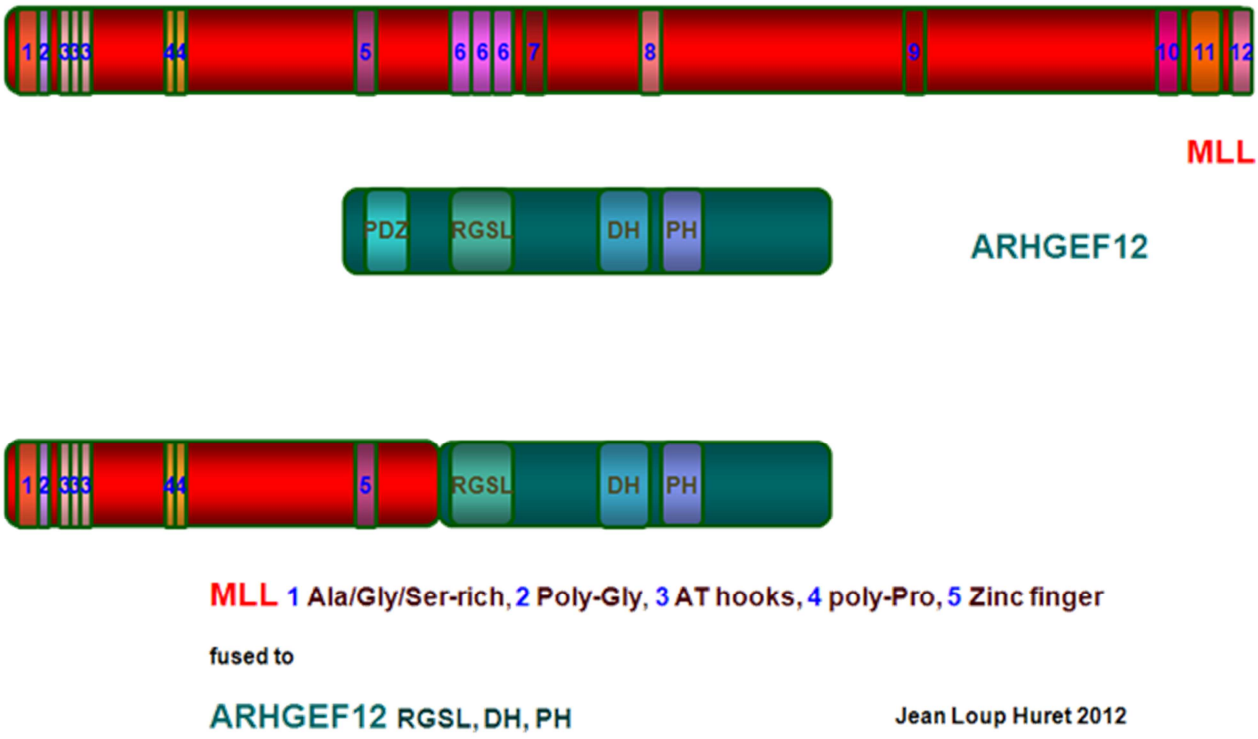
Location
11q23.3

Protein
A major transcript of 14982 bp produces a 3969 amino acids protein from 36 of the 37 exons. Contains from N-term to C-term a binding site for MEN1, 3 AT hooks (binds to the minor grove of DNA); 2 speckled nuclear localisation signals; 2 repression domains RD1 and RD2: RD1 or CXXC: cystein methyl transferase, binds CpG rich DNA, has a transcriptional repression activity; RD2 recruits histone desacetylases HDAC1 and HDAC2; 3 plant homeodomains (cystein rich zinc finger domains, with homodimerization properties), 1 bromodomain (may bind acetylated histones), and 1 plant homeodomain; these domains may be involved in protein-protein interaction; a FYRN and a FRYC domain; a transactivation domain which binds CBP; may acetylates H3 and H4 in the HOX area; a SET domain: methyltransferase; methylates H3, including histones in the HOX area for allowing chromatin to be open to transcription. MLL is cleaved by taspase 1 into 2 proteins before entering the nucleus: a p300/320 N-term protein called MLL-N, and a p180 C-term protein, called MLL-C. The FYRN and a FRYC domains of native MLL associate MLL-N and MLL-C in a stable complex; they form a multiprotein complex with transcription factor TFIID. General transcription factor; maintains HOX genes expression in undifferentiated cells. Major regulator of hematopoiesis and embryonic development; role in cell cycle regulation.

ARHGEF12

Location
11q23.3

Protein
Better known as LARG, ARHGEF12 contains a PDZ (postsynaptic density protein, Drosophila disc large tumor suppressor, and zonula occludens-1 protein) domain, which localize ARHGEF12 to the membrane, a regulator of G protein signalling-like domain (RGSL or RH), which binds to activated heterotrimeric G protein alpha12/13 subunits, a Dbl homology (DH) domain, responsible for exchange activity, and a pleckstrin homology (PH) domain, involved in the regulation of the process. Regulatory protein involved in the GDP/GTP exchange reaction of the Rho proteins; activates a Rho-GTPase-dependent signaling pathway; activated by FYN.



Result of the chromosomal anomaly

Hybrid gene

Description

5' MLL - 3' ARHGEF12

Fusion protein

Description

Joins amino acid 1362 from MLL to amino acid 309 from ARHGEF12. The fusion protein comprises the Ala/Gly/Ser-rich region, poly-Gly stretch, three AT hooks domains, poly-Pro stretches, and Zinc finger CXXC-type domain from MLL fused to the RGSL, DH, PH domains of ARHGEF12.

References

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Shih LY, Liang DC, Fu JF, Wu JH, Wang PN, Lin TL, Dunn P, Kuo MC, Tang TC, Lin TH, Lai CL. Characterization of fusion partner genes in 114 patients with de novo acute myeloid leukemia and MLL rearrangement. Leukemia. 2006 Feb;20(2):218-23

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